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Lisette Okkels Jensen MD DMSci, Michael Maeng, Bent Raungaard, Thomas Engstrøm MD DMSci, Henrik Steen Hansen MD DMSci, Svend Eggert Jensen, Hans Erik Bøtker MD DMSci, Johnny Kahlert, Jens Flensted Lassen, Evald Høj Christiansen

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Lisette Okkels Jensen MD DMSci PhD[1], Michael Maeng MD PhD[2], Bent Raungaard MD PhD[3], Thomas Engstrøm MD DMSci PhD[4], Henrik Steen Hansen MD DMSci[1], Svend Eggert Jensen MD PhD[3], Hans Erik Bøtker MD DMSci PhD[2], Johnny Kahlert MSc PhD[5], Jens Flensted Lassen MD PhD[4], Evald Høj Christiansen MD PhD[2]

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[1]Department of Cardiology, Odense University Hospital, Odense, Denmark
[2]Department of Cardiology, Aarhus University Hospital, Skejby Hospital, Aarhus, Denmark
[3]Department of Cardiology, Aalborg University Hospital, Aalborg, Denmark
[4]Department of Clinical Epidemiology, Aarhus University, Aarhus, Denmark
[5]Department of Cardiology, Rigshospitalet, University of Copenhagen, Copenhagen, Denmark

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Correspondence to:
Lisette Okkels Jensen, Professor DMSci, PhD, MD
Odense University Hospital
Department of Cardiology
Sdr. Boulevard 29
5000 Odense C
Denmark
E-mail: okkels@dadlnet.dk
Phone: +45 6541 2681

Abstract

Background: In patients with increased bleeding risk during dual antiplatelet therapy, the Biolimus A9-coated BioFreedom, a stainless steel drug-coated stent devoid of polymer, has shown superiority compared to a bare metal stent. The aim of this study was to investigate whether the polymer free biolimus A9-coated BioFreedom is non-inferior to a modern thin strut biodegradable polymer cobalt-chromium sirolimus-eluting Orsiro stent in an all-comers patient population treated with percutaneous coronary intervention.

Methods: The multicenter SORT OUT IX trial (NCT02623140) randomly assigned all-comers patients to treatment with the BioFreedom drug-coated stent or the biodegradable polymer Orsiro stent in 4 Danish University Hospitals. The primary endpoint target lesion failure (TLF) is a composite of cardiac death, myocardial infarction (not related to other than index lesion) or target lesion revascularization within 12 months. Clinically driven event detection based on Danish registries will be used and continue through five years. Assuming an event rate of 4.2% in each stent group, 1,563 patients in each treatment arm will provide 90% power to detect non-inferiority of the drug-coated BioFreedom stent with a non-inferiority margin of 2.1%.

Results: 3150 patients have been randomized and enrolled in the study.

Conclusion: The SORT OUT IX trial will determine whether the drug-coated BioFreedom stent is non-inferior to a modern biodegradable polymer Orsiro stent.

KEY WORDS: percutaneous coronary intervention, drug-eluting stent, outcome

INTRODUCTION

In percutaneous coronary intervention with drug-eluting stent, the durable polymer used for first and second generation drug-eluting stents has been suspected as a potential trigger of vessel wall inflammation and late adverse outcomes.[1] Hence newer generation drug-eluting stents with either biodegradable polymers or more biocompatible durable polymers, which have the potential to abolish these late events, have been developed.[2-5] The target lesion failure rate for the biodegradable polymer sirolimus-eluting Orsiro stent was non-inferior to the gold standard everolimus-eluting stents in the BIOSCIENCE[3] trial and non-inferior to the biodegradable polymer biolimus-eluting Nobori stent in the the SORT OUT VII trial.[6] A polymer free and carrier free biolimus A9-coated BioFreedom stent has been developed, which is a highly lipophilic sirolimus analogue that transfers the biolimus A9 into the vessel wall over a period of 1 month[7]. Compared to the biodegradable polymer sirolimus-eluting Orsiro stent, the stents properties differ in 1) the biolimus A9 BioFreedom stent is polymer free and the sirolimus-eluting Orsiro stent has a silicon carbide coating and a circumferential polymer coating where the polymer degradation is taking place after 12-24 months, 2) the biolimus A9 BioFreedom stent has thicker stent struts (120 µm compared to the 60-80 µm for the sirolimus-eluting Orsiro stent, 3) faster drug release (1 month versus 12 weeks). The BioFreedom stent has shown superiority to a bare-metal stent in patients treated with only one month of dual antiplatelet therapy[7, 8]. However, it has not previously been studied if the BioFreedom stent have similar outcome results as a modern drug-eluting stent. In the SORT OUT IX trial, we have designed a registry-based randomized controlled non-inferiority trial comparing the polymer free biolimus A9-coated BioFreedom stent with the sirolimus-eluting Orsiro stent in a population-based all-comers setting, using registry detection of clinically driven events.

METHODS

Patients and study design

SORT OUT IX is a randomized, multicenter, single-blind, all-comers, two-arm, non-inferiority trial comparing the polymer free biolimus A9-coated BioFreedom to the biodegradable polymer cobalt-chromium sirolimus-eluting Orsiro stent in patients treated with PCI. Patients were eligible, if they were at least 18 years old, had chronic stable coronary artery disease or acute coronary syndromes including ST-segment elevation myocardial infarction, and at least one coronary lesion with more than 50% diameter stenosis, requiring treatment with a drug-eluting stent. If multiple lesions were treated, the allocated study stent had to be used in all lesions. No restrictions were placed on number of treated lesions, number of treated vessels, or lesion length. Exclusion criteria were life expectancy of less than one year; an allergy to aspirin, clopidogrel, ticagrelor, sirolimus, or biolimus; participation in another randomized stent trial; or inability to provide written informed consent. The trial is registered with ClinicalTrials.gov, NCT02623140 and the study protocol was approved by the Danish Research Ethics Committee (S-20150132) and The Danish Data Protection Agency (15/47707).

Informed consent and randomization

Between December 2015 and April 2017, a total of 3,150 patients were randomly assigned to treatment with polymer free biolimus A9-coated BioFreedom or biodegradable polymer cobalt-chromium sirolimus-eluting Orsiro stent at 4 Danish sites, 3 sites in Western Denmark (Odense University Hospital, Aarhus University Hospital and Aalborg University Hospital) and the Copenhagen University Hospital (Rigshospital). All patients signed the informed consent before randomization. Patients were enrolled by the investigators and randomly allocated to treatment

groups after diagnostic coronary angiography and before percutaneous coronary intervention. Block randomization by centre (permuted blocks of random sizes (2/4/6)) was used to assign patients in a 1:1 ratio to receive the polymer free biolimus A9-coated BioFreedom stent (Biosensors, Morges, Switzerland) or the biodegradable polymer cobalt-chromium sirolimus-eluting Orsiro stent (Biotronik, Bülach, Switzerland). An independent organization computer-generated the allocation sequence, stratified by gender and presence of diabetes. Patients were assigned to treatment through a web based Trial Partner randomization system. While operators were not blinded, all individuals analyzing data were masked to treatment assignment.

Study procedures and antithrombotic therapy

The Orsiro stent was available in six diameters (2.25, 2.50, 2.75, 3.00, 3.50, and 4.00 mm) and nine lengths (9, 13, 15, 18, 22, 26, 30, 35 and 40 mm). The BioFreedom stent was available in six diameters (2.25, 2.50, 2.75, 3.00, 3.50 and 4.00 mm) and eight lengths (8, 11, 14, 18, 24, 28, 33 and 38mm). Stents were implanted according to standard techniques. Direct stenting without prior balloon dilation was allowed. Full lesion coverage was attempted by implanting one or more stents. Drug-eluting stents not specified by the random allocation scheme and bare metal stents were prohibited, unless the study stent could not be implanted. In such cases, other stents or balloon angioplasty alone were allowed. Before implantation, patients were treated with acetylsalicylic acid (loading dose of 300 mg) and loaded with either clopidogrel 600 mg, ticagrelor 180 or prasugrel 60 mg. Combination of dual antiplatelet therapy was left to the discretion of the participating center whereas the duration of dual antiplatelet therapy was recommended for 6 months in patients with stable angina pectoris and 12 months in patients with acute coronary syndromes. Unfractionated heparin dose (70-100 IU/kg) was administered before the procedure. Glycoprotein IIb/IIIa inhibitors or bivalirudin were used at the operator's discretion. All risk

factors, baseline information, and procedure data are typed into the Western Denmark Heart Registry (WDHR)[9], which contains detailed patient- and procedure-specific information on all coronary angiographies, coronary interventions and coronary bypass surgery performed at the three interventional and eight non-interventional cardiac centers in Western Denmark. For patients enrolled at Rigshospitalet (using another database system), the same variables were typed into a separate database and merged with data from the WDHR for patients enrolled at the other three centers.

Outcome measures

The primary end point *target lesion failure* (TLF) is a composite of cardiac death, myocardial infarction (MI) (not related to other than index lesion) or clinically indicated target lesion revascularization (TLR) within 12 months. Individual components of the primary end point comprise the secondary end points: cardiac death; MI; clinically indicated TLR; all death (cardiac and non-cardiac) and target vessel revascularization; definite, probable, possible, and overall stent thrombosis according to the Academic Research Consortium (ARC) definition[10]; and a patient-related composite end point (all death, all MI, or any revascularization). Clinical follow-up will be continued through 5 years.

Definitions

Cardiac death: any death due to an evident cardiac cause, any death related to percutaneous coronary intervention, an unwitnessed death, or death from unknown causes. *Myocardial infarction:* the universal definition used by the European Society of Cardiology, the American College of Cardiology, the American Heart Association, and the World Heart Federation.[11] Biomarkers were not routinely assessed before or after the index percutaneous

coronary intervention procedure. *Myocardial infarction not related to other than index lesion:* any myocardial infarction that is not clearly attributable to a non-target vessel.

Stent thrombosis: definite, probable or possible stent thrombosis, according to the ARC[10] definition.

Target vessel revascularization: any repeat percutaneous coronary intervention or surgical bypass of any segment within the entire major coronary vessel that was proximal or distal to a target lesion, including upstream and downstream branches, and the target lesion itself.

Target lesion revascularization: repeat revascularization caused by a more than 50% stenosis within the stent or within a 5 mm border proximal or distal to the stent. Target vessel and target lesion revascularization were clinically driven.

Comorbidity: For all patients, we obtained data on all hospital diagnoses from the Danish National Registry of Patients covering all Danish hospitals from 1977 until the implantation date.[12] We then computed Charlson Comorbidity Index score, which covers 19 major disease categories, including diabetes mellitus, heart failure, cerebrovascular diseases, and cancer.[13]

Clinically driven event detection was used to avoid study-induced re-interventions (Figure 1). Data on mortality, hospital admission, coronary angiography, repeat percutaneous coronary intervention, and coronary artery bypass surgery were obtained for all randomly allocated patients from the following national Danish administrative and healthcare registries: the Civil Registration System[14]; the Western Denmark Heart Registry[9, 15, 16]; and the Danish National Registry of Patients[12], which maintains records on all hospitalizations in Denmark.

The Danish National Health Service provides universal tax-supported health care, guaranteeing residents free access to general practitioners and hospitals. The Danish Civil Registration System has kept electronic records on gender, birthdate, residence, emigration date, and vital status changes since 1968[14], with daily updates; the 10-digit civil registration number

assigned at birth and used in all registries allows accurate record linkage. The Civil Registration System provided vital status data for our study participants and minimized loss to follow-up. The National Registry of Causes of Deaths and the Danish National Registry of Patients provided information on causes of death and diagnoses assigned by the treating physician during hospitalizations (coded according to the *International Classification of Diseases*, 10th revision [ICD-10]).[12]

This methodology has been used in previous SORT OUT III-VII publications.[6, 17-20] An independent event committee, masked to treatment group assignment during the adjudication process, reviewed all endpoints and source documents to adjudicate causes of death, reasons for hospital admission, and diagnosis of myocardial infarction. Two dedicated percutaneous coronary intervention operators at each participating centre reviewed independently cine films for the event committee to classify stent thrombosis, TLR and TVR (either with percutaneous coronary intervention or coronary artery bypass grafting).

Statistical analysis

In analyses of every end point, follow-up will continue until the date of an end point event, death, emigration, or 12 months after stent implantation, whichever comes first. Survival curves will be constructed based on time to events, accounting for the competing risk of death. Hazard ratios will be computed using Cox proportional hazards regression analysis. Patients treated with the Orsiro stent will be used as the reference group for the overall analyses. Subgroup analyses (diabetes and acute coronary syndrome) will be performed. Hazard ratios will be calculated for TLF at 12-month follow-up for pre-specified patient subgroups (based on baseline demographic and clinical characteristics). The intention-to-treat principle will be used in all analyses

Sample size

The trial is powered for assessing non-inferiority of the Biolimus A9-coated BioFreedom stent to thin strut biodegradable polymer cobalt-chromium sirolimus-eluting Orsiro stent with respect to the primary endpoint at 12 months. An event rate of 4.2% is assumed in each stent group. With a sample size of 1,563 patients in each treatment arm, a two-group large-sample normal approximation test of proportions with a one-sided 0.050 significance level will have 90% power to detect non-inferiority with a predetermined non-inferiority margin of 2.1%. The sample of size 1,563 in each treatment arm assumes 0% lost-to-follow-up rate given the use of the Civil Registration System. A total number of 3,150 patients will be enrolled.

Role of the funding source

This study is investigator initiated and supported with an equal unrestricted grants from Biotronik, Bülach, Switzerland and Biosensors Interventional Technologies Pte Ltd., Singapore. These companies did not have a role in study design, data collection, data analysis, or interpretation of results. They also did not have access to the clinical trial database or an opportunity to review the manuscript.

DISCUSSION

The SORT OUT IX trial will provide head-to-head randomized comparison of two modern DES with different designs: the Biolimus A9-coated BioFreedom, a stainless steel drug-coated stent devoid of polymer, and the thin strut biodegradable polymer cobalt-chromium sirolimus-eluting Orsiro stent. Compared to the biolimus A9 BioFreedom stent the biodegradable

polymer sirolimus-eluting Orsiro stent has a silicon carbide coating and a circumferential polymer coating where the polymer degradation is taking place, ultrathin cobalt-chromium stent struts and slower drug release. The sirolimus-eluting Orsiro stent has shown excellent efficacy and safety outcomes in several randomised clinical trials[3, 6, 21, 22] and is a particularly suitable reference device for comparative stent studies.

Among PCI treated patients with high risk for bleeding, the BioFreedom was superior to a similar bare metal stent (BMS), in patients treated with dual antiplatelet therapy for 1 month. Risks of myocardial infarction and target lesion revascularisatioin were significantly lower in the BioFreedom treated patients compared to patients treated with a BMS. In two third of the patient population age (>75 years) was one of the risk factors for high risk for bleeding. The 1-year rate of definite stent thrombosis were higher than seen with modern thinner strut DES[3, 6, 21-23]and three-fourth of the definite stent thrombosis occurred early when the patients were still on dual antiplatelet therapy without differences among the BioFreedom and the BMS treated patients. Safety and efficacy benefits of BioFreedom stent were maintained for 2 years.[8]

The optimal duration of dual antiplatelet therapy (DAPT) in patients treated with complex lesions and/or high bleeding risk patients remains undetermined, and in addition, new stent designs using a bioabsorbable polymer might allow shorter duration of DAPT. In a recent meta-analysis, the authors concluded, that stent type may partially affect the outcome, together with DAPT length.[24]

Our study use patient-driven event detection based on Danish registries.[25] This registry-based randomized clinical trial (RB-RCT) design has been used in all SORT OUT trials[6, 17-20], in the "Prevention of Contrast Induced Nephropathy with N-Acetyl Cysteine and/or Sodium Bicarbonate in Patients with ST-Segment Myocardial Infarction. A prospective, randomized, open-labelled trial" (CINSTEMI)[26] and in the "Thrombus Aspiration During ST-Segment Elevation

Myocardial Infarction" (TASTE) trial[27], and has received substantial interest as a way of undertaking large-scale, independent clinical trials. The SORT- OUT trials are the first known Registry-based Randomized Clinical Trial, world wide and introduced, also this new concept in the Nordic countries.

Advantages of this approach include a substantial reduction in the expense associated with a randomized trial because we are able to use the established registry infrastructure. Moreover, the study design provides data that are more comparable to real-life situations because of the absence of study-related intervention and participants will be exposed to the same clinical monitoring as nonstudy patients. Data on mortality (cardiac and noncardiac) are obtained from the Danish Civil Registration System[14], hospital admission for myocardial infarction from the Danish National Registry of Patients[12], and basic descriptive data, coronary angiography, repeat PCI, and coronary bypass surgery from the Western Denmark Heart Registry.[9] Patient-driven event detection based on Danish registries will result in a nearly 100% follow up unless the patients have emigrated, which the CPR registry obtain information about with current residence of all Danish citizens.

In a population-based health care database like the Western Denmark Heart Registry, data are collected for quality-control and administrative purposes. This may reduce certain forms of bias, such as nonresponse bias, recall bias, and bias from loss to follow-up, which may influence prognostic estimates.[28] Also, there are considerable costs associated with conducting an RCT. The Western Denmark Heart Registry contains detailed patient- and procedure-specific information on all coronary angiographies, coronary interventions and coronary bypass surgery performed at the three interventional centers in Western Denmark.

In Denmark, all citizens have a personal civil registration number assigned at birth or upon immigration.[14] This unique personal identifier allows linkage of individual-level information across registries and databases. The Danish Civil Registration System is updated daily, and

maintains records on date of birth, death, and current residence of all Danish citizens. The Danish National Registry of Patients[29] contains information on all admissions and outpatient visits to the 52 Danish hospitals. For each hospital admission, the registry records dates of admission and discharge, surgical procedures performed, and up to 20 diagnoses classified according to the International Classification of Diseases (ICD), eighth revision, until the end of 1993, and tenth revision thereafter.[12]

Like any conventional randomized trial, the SORT OUT trials use independent endpoint committee adjudication. Although the Danish health-care databases capture events of sufficient severity for patients to seek medical attention, these records might underestimate event rates compared with follow-up by dedicated trial staff.[30] However, this situation should not bias differences detected between treatment groups, and the negligible loss to follow-up probably compensated for this potential limitation.

Limitations

The primary endpoint is assessed after 1 year, and the TLF at 1 year may not predict the long term outcome with safety and efficacy after 5 years[31]. The clinical outcomes after implantation of drug-eluting stents have improved in recent years. Therefore we expect that the event rate in our study is representative of the real event rate among this patient population. Both study stents are available on the market, and even if one of the study stents will be replaced by a newer generation DES, both stent types have still been implanted in many patients, so the results with 1 year as well as long term follow-up will be relevant. All patients were recommended 6-12 months of DAPT. Bleeding complications are not registered and may be underreported with registry information. Non-inferiority testing in essence flips the traditional null and alternative hypotheses. Using this approach, the null hypothesis is that the new treatment is worse than the old treatment.

This means that rather than assuming that there is no difference, the null hypothesis is that a difference exists and that the new treatment is inferior. As in a traditional trial, the two conclusions available from the statistical tests are: reject or failure to reject the null hypothesis. Rejecting the null hypothesis is making the statement that the new treatment is not worse than the old treatment. This implies that the new treatment is as good or even better that the old.

Conflict of interest statement

LOJ has received research grants from Terumo, Biotronik, St Jude Medical, and Biosensors to her institution and honoraria from Biotronik. EHC has received research grants Biotronik and Biosensors to his institution. MM has received lecture and/or consulting fees from Bayer, Novo Nordisk, Bristol-Myers Squibb, Boehringer-Ingelheim, Astra-Zeneca, and a research grant from Volcano (now Philips). JFL has received research grants from Biotronik and Biosensors to his institution. BR, TE, HSH, SEJ, HEB and JK report no conflicts of interest.

Sort Out IX Study Group

Principal Investigators: Lisette Okkels Jensen

Steering Committee: Lisette Okkels Jensen (co-chair), Evald Høj Christiansen (co-chair), Hans Erik Bøtker, Svend Eggert Jensen, Bent Raungaard, Thomas Engstroem, Jens Flensted Lassen, Henrik Steen Hansen.

Coordinating Center: The Scandinavian Organization for Randomised Trials with Clinical Outcome (SORT OUT), Aarhus University Hospital, Skejby, Aarhus, Denmark

Clinical Events Committee: Kristian Thygesen, Jacob Thorsted Sørensen, Bjarne Linde Noergaard Aarhus, Denmark

Data and Monitoring Center: Johnny Kahlert (Biostatistican) Clinical Epidemiology, Aarhus University Hospital, Aarhus, Denmark

Reference list

1. Morice MC, Serruys PW, Sousa JE, Fajadet J, Ban HE, Perin M, et al. A randomized comparison of a sirolimus-eluting stent with a standard stent for coronary revascularization. N Engl J Med 2002;346(23):1773-1780.
2. Hamon M, Niculescu R, Deleanu D, Dorobantu M, Weissman NJ, Waksman R. Clinical and angiographic experience with a third-generation drug-eluting Orsiro stent in the treatment of single de novo coronary artery lesions (BIOFLOW-I): a prospective, first-in-man study. EuroIntervention 2013;8(9):1006-1011.
3. Pilgrim T, Heg D, Roffi M, Tuller D, Muller O, Vuilliomenet A, et al. Ultrathin strut biodegradable polymer sirolimus-eluting stent versus durable polymer everolimus-eluting stent for percutaneous coronary revascularisation (BIOSCIENCE): a randomised, single-blind, non-inferiority trial. Lancet 2014;384(9960):2111-2122.
4. Smits PC, Hofma S, Togni M, Vazquez N, Valdes M, Voudris V, et al. Abluminal biodegradable polymer biolimus-eluting stent versus durable polymer everolimus-eluting stent (COMPARE II): a randomised, controlled, non-inferiority trial. Lancet 2013;381(9867):651-60.
5. Windecker S, Serruys PW, Wandel S, Buszman P, Trznadel S, Linke A, et al. Biolimus-eluting stent with biodegradable polymer versus sirolimus-eluting stent with durable polymer for coronary revascularisation (LEADERS): a randomised non-inferiority trial. Lancet 2008;372(9644):1163-1173.
6. Jensen LO, Thayssen P, Maeng M, Ravkilde J, Krusell LR, Raungaard B, et al. Randomized Comparison of a Biodegradable Polymer Ultrathin Strut Sirolimus-Eluting Stent With a Biodegradable Polymer Biolimus-Eluting Stent in Patients Treated With Percutaneous Coronary Intervention: The SORT OUT VII Trial. Circ Cardiovasc Interv 2016;9(7).
7. Urban P, Meredith IT, Abizaid A, Pocock SJ, Carrie D, Naber C, et al. Polymer-free Drug-Coated Coronary Stents in Patients at High Bleeding Risk. N Engl J Med 2015;373(21):2038-47.
8. Garot P, Morice MC, Tresukosol D, Pocock SJ, Meredith IT, Abizaid A, et al. 2-Year Outcomes of High Bleeding Risk Patients After Polymer-Free Drug-Coated Stents. J Am Coll Cardiol 2017;69(2):162-171.
9. Schmidt M, Maeng M, Madsen M, Sorensen HT, Jensen LO, Jakobsen CJ. The Western Denmark Heart Registry: Its Influence on Cardiovascular Patient Care. J Am Coll Cardiol 2018;71(11):1259-1272.
10. Cutlip DE, Windecker S, Mehran R, Boam A, Cohen DJ, Van Es GA, et al. Clinical end points in coronary stent trials: a case for standardized definitions. Circulation 2007;115(17):2344-2351.
11. Thygesen K, Alpert JS, Jaffe AS, Simoons ML, Chaitman BR, White HD, et al. Third universal definition of myocardial infarction. Eur Heart J 2012;33(20):2551-2567.
12. Andersen TF, Madsen M, Jorgensen J, Mellemkjoer L, Olsen JH. The Danish National Hospital Register. A valuable source of data for modern health sciences. Dan Med Bull 1999;46(3):263-268.

13. Charlson ME, Pompei P, Ales KL, MacKenzie CR. A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. J Chronic Dis 1987;40(5):373-383.
14. Frank L. Epidemiology. When an entire country is a cohort. Science 2000;287(5462):2398-2399.
15. Jensen LO, Maeng M, Kaltoft A, Thayssen P, Hansen HH, Bottcher M, et al. Stent thrombosis, myocardial infarction, and death after drug-eluting and bare-metal stent coronary interventions. J Am Coll Cardiol 2007;50(5):463-70.
16. Schmidt M, Maeng M, Jakobsen CJ, Madsen M, Thuesen L, Nielsen PH, et al. Existing data sources for clinical epidemiology: The Western Denmark Heart Registry. Clin Epidemiol 2010;2:137-144.
17. Jensen LO, Thayssen P, Hansen HS, Christiansen EH, Tilsted HH, Krusell LR, et al. Randomized comparison of everolimus-eluting and sirolimus-eluting stents in patients treated with percutaneous coronary intervention: the Scandinavian Organization for Randomized Trials with Clinical Outcome IV (SORT OUT IV). Circulation 2012;125(10):1246-55.
18. Rasmussen K, Maeng M, Kaltoft A, Thayssen P, Kelbaek H, Tilsted HH, et al. Efficacy and safety of zotarolimus-eluting and sirolimus-eluting coronary stents in routine clinical care (SORT OUT III): a randomised controlled superiority trial. Lancet 2010;375(9720):1090-1099.
19. Raungaard B, Jensen LO, Tilsted HH, Christiansen EH, Maeng M, Terkelsen CJ, et al. Zotarolimus-eluting durable-polymer-coated stent versus a biolimus-eluting biodegradable-polymer-coated stent in unselected patients undergoing percutaneous coronary intervention (SORT OUT VI): a randomised non-inferiority trial. Lancet 2015;385(9977):1527-35.
20. Christiansen EH, Jensen LO, Thayssen P, Tilsted HH, Krusell LR, Hansen KN, et al. Biolimus-eluting biodegradable polymer-coated stent versus durable polymer-coated sirolimus-eluting stent in unselected patients receiving percutaneous coronary intervention (SORT OUT V): a randomised non-inferiority trial. Lancet 2013;381(9867):661-669.
21. Kandzari DE, Mauri L, Koolen JJ, Massaro JM, Doros G, Garcia-Garcia HM, et al. Ultrathin, bioresorbable polymer sirolimus-eluting stents versus thin, durable polymer everolimus-eluting stents in patients undergoing coronary revascularisation (BIOFLOW V): a randomised trial. Lancet 2017;390(10105):1843-1852.
22. von Birgelen C, Kok MM, van der Heijden LC, Danse PW, Schotborgh CE, Scholte M, et al. Very thin strut biodegradable polymer everolimus-eluting and sirolimus-eluting stents versus durable polymer zotarolimus-eluting stents in allcomers with coronary artery disease (BIO-RESORT): a three-arm, randomised, non-inferiority trial. Lancet 2016;388(10060):2607-2617.
23. Urban P, Abizaid A, Chevalier B, Greene S, Meredith I, Morice MC, et al. Rationale and design of the LEADERS FREE trial: A randomized double-blind comparison of the BioFreedom drug-coated stent vs the Gazelle bare metal stent in patients at high bleeding risk using a short (1 month) course of dual antiplatelet therapy. Am Heart J 2013;165(5):704-709.
24. D'Ascenzo F, Iannaccone M, Saint-Hilary G, Bertaina M, Schulz-Schupke S, Wahn Lee C, et al. Impact of design of coronary stents and length of dual antiplatelet therapies on ischaemic and bleeding events: a network meta-analysis of 64 randomized controlled trials and 102 735 patients. Eur Heart J 2017;38(42):3160-3172.

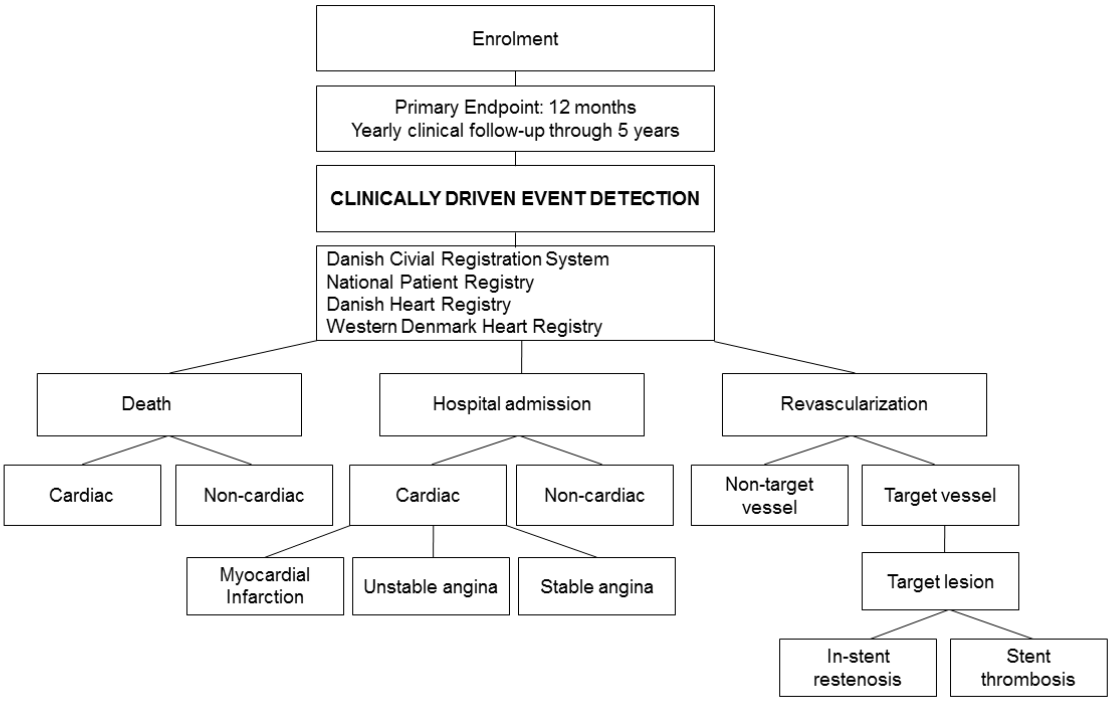
25. Thuesen L, Jensen LO, Tilsted HH, Maeng M, Terkelsen C, Thayssen P, et al. Event detection using population-based health care databases in randomized clinical trials: a novel research tool in interventional cardiology. Clin Epidemiol 2013;5:357-61.
26. Thayssen P, Lassen JF, Jensen SE, Hansen KN, Hansen HS, Christiansen EH, et al. Prevention of contrast-induced nephropathy with N-acetylcysteine or sodium bicarbonate in patients with ST-segment-myocardial infarction: a prospective, randomized, open-labeled trial. Circ Cardiovasc Interv 2014;7(2):216-224.
27. Frobert O, Lagerqvist B, Olivecrona GK, Omerovic E, Gudnason T, Maeng M, et al. Thrombus aspiration during ST-segment elevation myocardial infarction. N Engl J Med 2013;369(17):1587-1597.
28. Sorensen HT, Lash TL, Rothman KJ. Beyond randomized controlled trials: a critical comparison of trials with nonrandomized studies. Hepatology 2006;44(5):1075-1082.
29. Juel K, Helweg-Larsen K. The Danish registers of causes of death. Dan Med Bull 1999;46(4):354-357.
30. Webster MW, Ormiston JA. Sorting out drug-eluting stents. Lancet 2010;375(9720):1060-1062.
31. Maeng M, Tilsted HH, Jensen LO, Krusell LR, Kaltoft A, Kelbaek H, et al. Differential clinical outcomes after 1 year versus 5 years in a randomised comparison of zotarolimus-eluting and sirolimus-eluting coronary stents (the SORT OUT III study): a multicentre, open-label, randomised superiority trial. Lancet 2014;383(9934):2047-56.

Figure legend

Figure 1

Clinically driven event registration

Figure 1



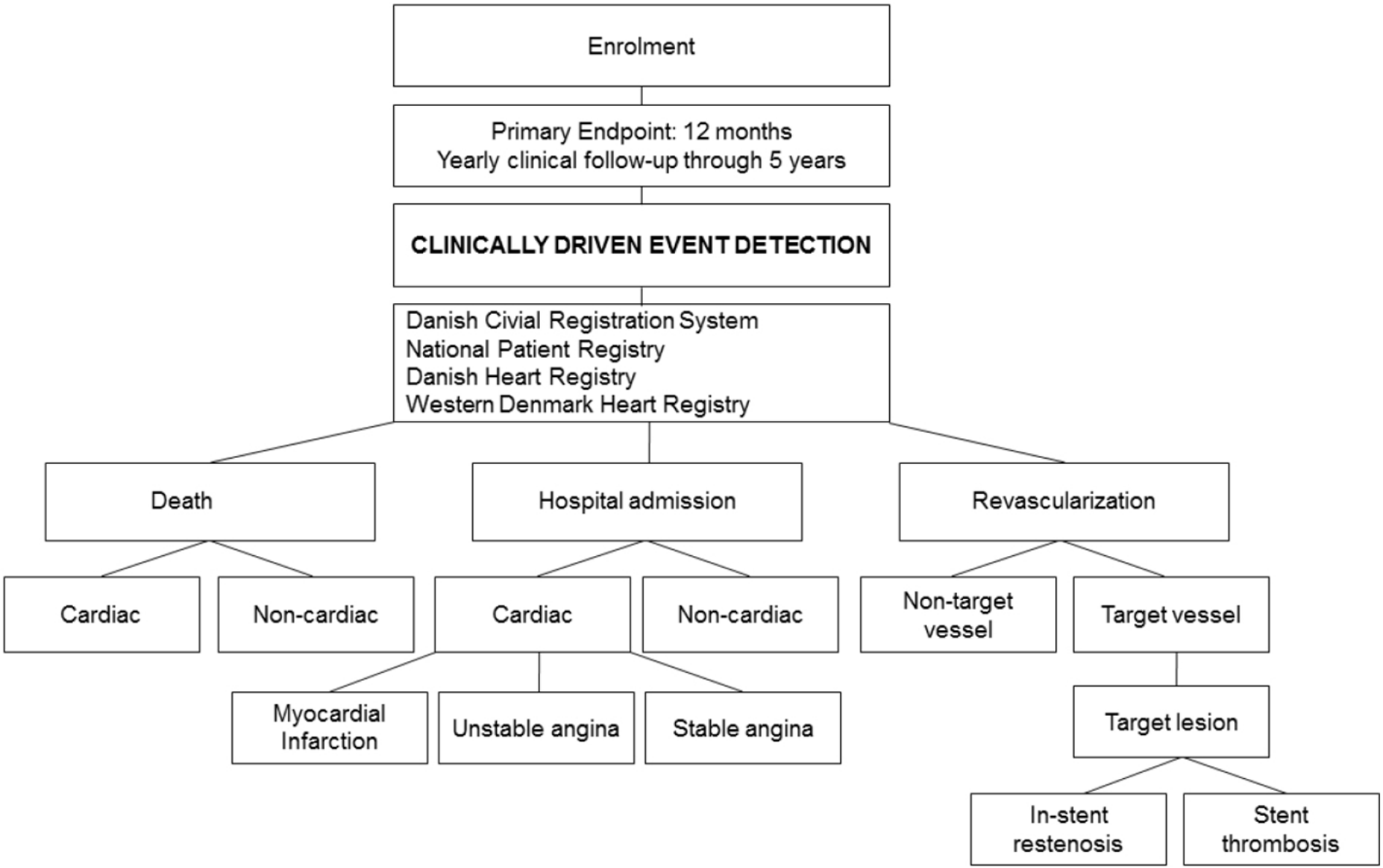

Enrolment
Primary Endpoint: 12 months
Yearly clinical follow-up through 5 years
CLINICALLY DRIVEN EVENT DETECTION
Danish Civial Registration System
National Patient Registry
Danish Heart Registry
Western Denmark Heart Registry
Death
Hospital admission
Revascularization
Cardiac
Non-cardiac
Cardiac
Non-cardiac
Non-target vessel
Target vessel
Myocardial Infarction
Unstable angina
Stable angina
Target lesion
In-stent restenosis
Stent thrombosis

Figure 1